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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,753	01/23/2002	Sergei Bavykin	0003/00377	9563

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,753	BAVYKIN ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on September 1, 2005.

Preliminary Remark

Claims 1-18 are pending and are under prosecution herein.

Applicants are advised that the petition to claim priority to 09/751,654, now a U.S. Patent No. 6,818,398, with reasons of unintentially claimed delay, has been **Granted**.

Claim Rejections - 35 USC § 112 – Necessitated by Amendment

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

Claims 1 and 9 (and their dependent claims 2-8 and 10-18, respectively) have been amendment to an embodiment which connotes that the labeling occurs at 5' or the 3' end of the nucleic acid molecule.

There is no justification or support for this concept in the specification as filed.

Pages 7 and 8 appear to disclose that method does contemplate have evidence that labeling occurs mostly on the ends of the nucleic acid, while having randomly incorporated labels within the

molecule, does not have any example or literal support for a method that contemplates a method which produces labels exclusively at the nucleic acids termini.

Removal of new matter is requested.

Claim Rejections - 35 USC § 102

The rejection of claims 1-13 and 16-18 under 35 U.S.C. 102(e) as being anticipated by Bavykin et al. (US 2003/0096229 A1), now a U.S. Patent No. 6,818,398 B2 (issued November 16, 2004; herein, the '398 patent), made in the Office Action mailed on March 29, 2005 is withdrawn in view of the granting of the petition to claim priority to the '398 patent.

The rejection of claims 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Bavykin et al. (US 2003/0096229 A1, now a U.S. Patent no. 6,818,398) in view of Sheldon et al. (U.S. Patent No. 4,617,261, issued October 14, 1986), made in the Office Action mailed on March 29, 2005 is withdrawn in view of the granting of the petition to claim priority to the '398 patent. Since the '398 patent is not prior art, the rejection must fall.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-12, 14, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirzabekov et al. (U.S. Patent No. 5,981,734, November 9, 1999, filed July 17,

1997) in view of Guillet et al. (WO 99/22020, published May 6, 1999), made in the Office Action mailed on March 29, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on September 1, 2005 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Mirzabekov et al. disclose a method of labeling DNA or RNA, wherein said method involves the following steps:

(a) generating a free aldehyde group on a DNA via process of depurination (column 4, lines 34-35) or on an RNA via process of oxidation of the 3' terminal ribonucleoside with sodium periodate (column 4, lines 36-37);

(b) the free-aldehyde group of the DNA or RNA is reacted with hydrazine (primary amine) of the fluorescent labels via nucleophilic addition reaction (column 4, lines 37-39; column 5, lines 5-6), thereby producing a labeled DNA or RNA.

The resulting hydrazone bond is disclosed as being stabilized by *reduction* with sodium cyanoborohydride (column 4, lines 39-40), and particularly, $NaCNBH_3$ (column 3, lines 8-9).

With regard to claim 4, Mizabekov et al. disclose that ethylenediamine was shown to be "particularly effective" in the quantitative scission of depurination of DNA, wherein ethylenediamine with depurinated DNA sites also introduced a reactive primary amino group that is subsequently used for fluorescent labeling by reaction with commercially available activated fluorophores (column 6, lines 16-21).

With regard to claim 7, as the fluorescent labels comprising hydrazine group is reacted with the free aldehyde group, the step reducing the condensation product and cross-linking the reduced condensation product with a label is necessarily achieved in one reaction step.

Mirzabekov et al., in generating the free aldehyde group on the DNA or RNA do not employ the reagents hydrogen peroxide in combination with the coordination complex recited in claim 3.

Guillet et al. disclose a method of generating free redicals in nucleic acid molecules (DNA or RNA) via free-radical mechanism (page 3, lines 29-30; page 8, line 24). Guillet et al., in generating free radicals in nucleic acid molecules, employ γ irradiation (page 14, lines 3-5; page 15, lines 17-20), as well as chemical reagents such as hydrogen peroxide (page 16, lines 4-5). Guillet et al. also disclose that it is common to add catalysts/accelerators to hydrogen peroxide to improve the yield of free radicals, particularly Fenton's reagents (Fe^{2+}/H_2O_2) (page 18, lines 3-4; page 33, lines 24-28), catalyzing the reaction as recited below:

$$H_2O_2 + H^+ + Fe^{2+} \rightarrow {}^{\bullet}OH + H_2O + Fe^{3+}$$

The generation of the free radicals (i.e., reaction condition) is disclosed as being conducted at room temperature (thus below the boiling point of water as well as being between 0°C and 95°C (page 20, lines 15-16).

Guillet et al. disclose that single stranded DNA molecules from Sigma®, which are denatured in 1.02% aqueous solution were employed (page 20, lines 6-10). While Guillet et al. are not explicit the description of the aqueous solution containing the single-stranded DNA molecules, it is assumed that the aqueous solution contains denaturing (or double-strand weakening) agent.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made employ the well-known reaction reagents of Guillet et al. to produce nucleic acids comprising free aldehyde group of Mirzabekov et al. for the following reasons.

Mirzabekov et al., while not explicit, disclose a critical feature of their invention, which would have motivated a one of skill in the art:

"A feature of the invention is the ***chemical modification*** of the terminus or internal residues of the molecules for ***subsequent*** attachment of different labels. An ***advantage*** of the invention is that the ***efficiency*** of the labeling is independent of the oligonucleotide length." (column 2, lines 23-27)

Mizabekov et al. continue :

"A feature of the invention is direct fluorescent labeling of DNA and RNA. An ***advantage*** of the invention is that the labeling method can be applied to both DNA and RNA, either isolated from cells or synthesized..."

The critical feature is disclosed as, "modifying the nucleic acid molecules to ***create a region having an active center, and contacting a dye to the active center so as to cause attachment of said dye to the active center***. One embodiment of the method is modifying the ***nucleic acid to create a nucleophilic region (e.g., a region containing a primary amino group***)...and ***contacting an activated fluorescent dye with the region so as to cause addition of the fluorescent label to the region***." (column 2, line 62 through column 3, line 4).

While Mirzabekov et al. are not explicit in every well known method which would produce a nucleophilic reagion (or free radical containing region) on a nucleic acid molecules, given such disclosure, one of ordinary skill in the art would have been reasonably motivated to employ well-known methods of producing free aldehyde region (or free radical region) on a nucleic acid, such as

Fenton reagents disclosed by Guillet et al., employing hydrogen peroxide with transition metal ion complex to arrive at the claimed invention.

One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success at producing this combination as Mirzabekov et al. make clear that so long as free aldehyde region (or free radical region) is produced in a nucleic acid molecule, the reduction of said region through amine and fluorescently labeling would have been produced.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants contend that inasmuch as Guillet et al. cannot work with fractionation and inasmuch as Mirzabekov et al. requires fractionization, the combination is impermissible (page 7, top paragraph, Response).

Applicants state that the invention described by Guillet is to keep long DNA molecules intact while labeling the polymer along the backbone. Applicants point to the labeling process disclosed by Guillet et al., wherein the process of labeling a polymer with functional groups randomly distributed along the polymer backbone chain, arguing that the label is present within the nucleotide backbone (i.e., 136, 77, and 48th nucleotides; *see* page 7, 2nd paragraph; Respone).

Applicants state that the process disclosed by Guillet et al. is used for, "PCR chain extensions, and to allow the sequencing of the NA [nucleic acid] of high molecular weight." (page 7, 2nd paragraph, Response).

Applicants' position is that because the method disclosed by Mirzbekov et al. is for labeling short nucleic acid fragments while the method disclosed by Guillet et al. is for labeling a long nucleic acid molecule, the combination would not be permissible in that there is no motivation to combine the teachings, wherein the teachings have "inapposite goals." (page 7, 4th paragraph, Response).

These arguments are not found persuasive.

It should be pointed out that Mirzabekov et al. while does label nucleic acids for hybridization, do not limit their teachings to "short" nucleic acid fragments, as Applicants contend.

Specifically, on column 4, lines 59-64, the artisans explicitly state that the method of their invention is useful for labeling molecules containing, "more than 1,500 nucleotides." Clearly, 1,500 nucleotides are not "short," fragments.

Secondly, while Applicants, by way of their amendment, connote that the instantly claimed method is drawn to end labeling the nucleic acids, "either on the 5' or the 3' end of the molecules at the site of scission," the breadth of the claims allow for the labels to be attached throughout the molecule, so long as there is at least a label at either on the 5' or the 3' end of the molecule.

As Applicant' are correct in stating, that the method disclosed by Guillet et al. who employ hydrogen peroxide in their labeling method, label a polymer with functional groups randomly distributed along the polymer backbone chain; and in their statement that the label is present within the nucleotide backbone. However, it appears that Applicants' interpretation of the term, "randomly" excludes ends of the nucleic acid fragments. This is interpretation is erroneous.

It is asserted that the treatment of a nucleic acid molecule will necessarily produce free aldehyde moieties, not only within the nucleic acid molecule, but also at the ends of the molecule as well (hence, "random").

This fact is even supported by Applicants' own specification wherein Applicants' method which employ hydrogen peroxide for labeling, state:

> The inventors have found that radical mediated labeling seems to be an effective method for placing the majority of the dye on the ends of the nucleic acid fragments.

-page 7, lines 39 and 40

3'-end of the nucleic acid strand. In addition, the inventors found that in OP-Cu-mediated protein-DNA crosslinking, the crosslinking occurs at the 5'-end or the 3'-end of the DNA molecule in approximately 90% of the cross-linked complexes, and crosslinking occurs randomly along the DNA fragment in approximately 10% of the complexes.

-page 8, lines 2-6

Clearly, the method of Guillet et al. who treat nucleic acid molecules with the same agent as the claims (hydrogen peroxide) would produce free-aldehyde moieties, randomly across, including the ends of the nucleic acid molecule.

Finally, with regard to Applicants' statement regarding the impermissible combination of the two references for having inapposite goals, this argument is not found persuasive because the goals of the two inventors are in labeling a nucleic acid molecule, and not employing short and long nucleic acid molecules as Applicants' intend to contend.

This fact is evidenced by the disclosure made by Mirzabekov et al. who state that nucleic acid comprising more than 1,500 nucleotides can be labeled. In addition, were Applicants' rationalization to be correct, a method of labeling a short nucleic acid fragment with a fluorescent moiety would not be obvious over a method of sequencing a long nucleic acid with the same fluorescent moiety, because the two methods have inapposite goals – labeling a short versus a long nucleic acid.

Clearly, such rationalization is flawed.

The invention as claimed is obvious over the cited references, and the rejection is maintained.

Applicants are advised that the specification, on page 8, appear to disclose a non-obvious embodiment wherein OP-Cu mediated protein-DNA crosslinking (i.e., labeling) produced 90% of the labeling (cross-linking) at either the 3' or the 5' end of the nucleic acid molecule. An amendment

to include this embodiment in the base claims would render the entire application in condition for allowance.

The rejection of claim 15 under 35 U.S.C. 103(a) as being unpatentable over Mirzabekov et al. (U.S. Patent No. 5,981,734, November 9, 1999, filed July 17, 1997) in view of Guillet et al. (WO 99/22020, published May 6, 1999) as applied to claims 1-12, 14, 16, and 17 above, and further in view of Fuller et al. (U.S. Patent No. 5,314,595, issued May 24, 1994), made in the Office Action mailed on March 29, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on September 1, 2005 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

The teachings of Mirzabekov et al. and Guillet et al. have already been discussed above.

Mirzabekov et al. and Guillet et al. do not explicitly discuss the well-known denaturing reagents of double-stranded nucleic acid recited in claim 15.

Fuller et al. evidences that reagents such as urea are well-known DNA denaturing reagent, commonly employed in biotechnology art (column 4, lines 55-56).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ any of well-known denaturing reagents, such as that of Fuller et al. to produce a single stranded nucleic acid molecule for labeling method of Mirzabekov et al. and Guillet et al. for the following reasons.

The method of Mirzabekov et al. and Guillet et al. is drawn to a method of labeling a single-stranded nucleic acid molecules (such as DNA or RNA). Since the artisans employ single-stranded nucleic acids in their labeling method, one of ordinary skill in the art at the time the invention was

made would have been clearly motivated to employ any of the well-known denaturing reagents, such as urea of Fuller et al., to first denature the double stranded nucleic acid prior to subjecting them to the single stranded nucleic acid labeling method of Mirzabekov et al. and Guillet at al. with a reasonable expectation of success.

Therefore the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants' rely on their arguments presented in the obviousness rejection based on the combination of Mizabekov et al. and Guilllet et al., the arguments of which had fully been addressed above.

Since Applicants do not make any new arguments for the instant rejection, the rejection is maintained for the reasons of record.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

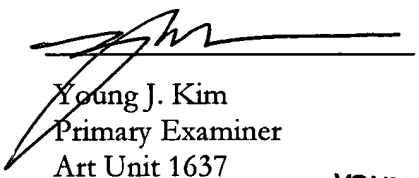
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.



Young J. Kim
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6/14/2006

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